REMARKS

Reconsideration and reexamination of this application are respectfully requested.

A. Interview Summary

Applicants thank the Examiner for the courtesy extended to their undersigned representative at the interview on March 17, 2009.

M.P.E.P. 713.04 provides eight items (A-H) that should be addressed in Applicant's submission of the substance of the interview. Applicant's submissions regarding each of those items follow.

(A) The only exhibit shown at the interview was the Smithies article attached hereto as Exhibit 1.

(B) All of the claims were generally discussed.

(C) The prior art discussed at the interview is the Nandi reference.

(D) The discussed amendments are reflected in the listing of claims provided herein. The listing of claims also includes additional amendments, not discussed at the interview, to specify that the "insertion DNA sequence" is a "heterologous" sequence.

(E) The principal argument presented by the undersigned at the interview was, as described in Examiner Shen's Interview Summary, that Nandi does not disclose vectors within the scope of the claims. Applicant disagrees with the Examiner's conclusion regarding that argument that is stated in the Interview Summary.

(F) No other pertinent matters were discussed.

(G) The outcome of the interview was that no agreement was reached.

(H) This interview was in person, so this item does not apply.

B. Status of Claims

Claims 71, 76, and 77 are amended. Claims 71-77 are pending and stand rejected.

The claims have been amended to use the term "flanking DNA sequence". As recited in the amended claims, the structure of the claimed constructs is such that,

> upon introduction of the DNA construct into the mammalian cell, the first flanking DNA sequence recombines with the homologous first endogenous DNA sequence in the genome of the mammalian cell, and the second flanking DNA sequence recombines with the homologous second endogenous DNA sequence in the genome of the mammalian cell, such that the first and second heterologous insertion DNA sequences are inserted into the genome of the mammalian cell between the first and second endogenous DNA sequences.

That amendment is supported at page 4, lines 9-13, for example.

The claims have also been amended to specify that the first and second insertion DNA sequences are each "heterologous insertion DNA sequence[s]". That term is supported at page 4, lines 14-15, for example. That term defines the insertion DNA sequences as sequences that are different than or foreign to the recipient gene, as explained in the application. It also makes explicit that, unlike the "flanking DNA sequences," the heterologous insertion DNA sequences are not "homologous to endogenous DNA sequences in the genome of a mammalian cell."

C. Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 71-77 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Action at Item 2. Specifically, the Examiner was concerned that the phrase "and wherein, the first and second recombination DNA sequences direct

homologous recombination events between the first and second endogenous DNA sequences in the genome of the mammalian cell upon introduction of the DNA construct into the mammalian cell, such that the first and second insertion DNA sequences are inserted into the genome of the mammalian cell between the first and second endogenous DNA sequences" is unclear. In response, Applicant notes that that phrase is not present in the amended claims. Applicant respectfully submits that the amended claims are clear and that this rejection should be withdrawn.

D. Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 71-77 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly introducing new matter and as allegedly not enabled. Action at Items 3 and 4. Specifically, with respect to each rejection, the Examiner contends that the phrase "and wherein, the first and second recombination DNA sequences direct homologous recombination events between the first and second endogenous DNA sequences in the genome of the mammalian cell upon introduction of the DNA construct into the mammalian cell, such that the first and second insertion DNA sequences are inserted into the genome of the mammalian cell between the first and second endogenous DNA sequences" is new matter and renders the claims non-enabled. In response, Applicant notes that the phrase is not present in the amended claims, so these rejections are moot.

Instead, the amended claims recite:

> upon introduction of the DNA construct into the mammalian cell, the first flanking DNA sequence recombines with the homologous first endogenous DNA sequence in the genome of the mammalian cell, and the second flanking DNA sequence recombines with the homologous second

> endogenous DNA sequence in the genome of the mammalian cell, such that the first and second heterologous insertion DNA sequences are inserted into the genome of the mammalian cell between the first and second endogenous DNA sequences.

Applicant respectfully submits that the new phrase is fully supported by the application as filed and does not introduce new matter. Furthermore, the claims are enabled by the application as filed which demonstrates how to make and use vectors with the recited attributes. Accordingly, this rejection should be withdrawn.

E. Rejections Under 35 U.S.C. § 103(a)

Various groupings of claims 71-77 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Mansour et al., "Introduction of a lacZ reporter gene into the mouse int-2 locus by homologous recombination," *Proc Natl Acad Sci USA*. 87(19):7688-92, 1990 ("Mansour") in combination with various additional references. Action at Items 5-9. Applicants traverse those rejections.

Each of the rejections for alleged obviousness over Mansour in combination with other references depend on the disclosure of Mansour. However, Mansour is not prior art to this application, as Applicants demonstrated in their previous Response. Specifically, this application is a continuation of Application No. 10/639,754, filed August 13, 2003, which is a continuation of Application No. 08/466,699, filed June 6, 1995 (now Patent No. 6,638,768), which is a continuation of Application No. 08/301,037, filed September 6, 1994, (now Patent No. 6,528,313), which is a continuation of Application No. 08/048,056, filed April 19, 1993, which is a continuation of Application No. 07/598,679, which was filed on March 19, 1990, as PCT/FR90/00185, and which claimed the benefit of priority to FR 89 03630, filed March 20, 1989. The amended

claims are fully supported in FR 89 03630. Therefore, the priority date of this application is March 20, 1989, and the United States filing date is March 19, 1990. Mansour was published after both of those dates, in October of 1990.

Because Mansour is not prior art to this application, the rejections for alleged obviousness over Mansour in combination with other references should be withdrawn.

Various groupings of claims 71-77 also stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Nandi et al., *Proc Natl Acad Sci USA.*, Vol. 85, No. 11, pp. 3845-3849 (1988) ("Nandi"), in combination with various other references. Action at Items 10-14. Applicants traverse those rejections.

The Examiner characterizes Nandi as disclosing

> regulated expression of genes inserted at the human chromosomal beta-globin locus by homologous recombination by transfecting mammalian cells with a plasmid carrying a modified human beta-globin gene and a foreign gene composed of the coding sequence of the bacterial neomycin-resistance gene linked to simian virus 40 transcription signals (*SVneo*), and stable transformed cells were obtained in which the two genes are integrated at the beta-globin locus on human chromosome 11, and the genes inserted at the beta-globin locus were induced during differentiation.

The Examiner acknowledges that Nandi does not disclose the specific first gene products recited in the pending claims. However, the Examiner cites additional references that he seeks to combine with Nandi to allegedly render the claims obvious. Applicants respectfully disagree.

Nandi cites Smithies et al., *Nature*, Vol. 317, pp. 230-234 (1985) ("Smithies") for further details of the vector used in the work reported in Nandi. A copy of Smithies is

attached hereto as Exhibit 1. As shown in Smithies, the vector used by Nandi is different than the vectors defined by the pending claims.

The claimed vectors comprise both "a first heterologous insertion DNA sequence and a second heterologous insertion DNA sequence." In the claimed vectors "the first heterologous insertion DNA sequence encodes a first gene product that does not confer resistance to a selection agent involved in the selection of transformants" and "the second heterologous insertion DNA sequence encodes a second gene product that confers resistance to a selection agent involved in the selection of transformants." In contrast, the only heterologous DNA sequence in the vectors of Smithies (and thus Nandi), that encodes a gene product, is the one that encodes a gene product that confers resistance to a selection agent involved in the selection of transformants. Thus, the Nandi vector does not comprise a first heterologous insertion DNA sequence encoding a first gene product that does not confer resistance to a selection agent involved in the selection of transformants.

To be sure, the Nandi vector does comprise a partial coding sequence of human beta-globin. That sequence is homologous to endogenous sequences at the locus being targeted. Therefore, that sequence is part of a flanking DNA sequence homologous to an endogenous DNA sequence in the genome of a mammalian cell, and that sequence is not a "heterologous insertion DNA sequence" as recited in the amended claims. For that reason Nandi does not disclose every element of the pending claims.

The deficiencies of Nandi are not remedied by the other cited references. The other references are cited as disclosing DNA sequences encoding different types of

gene products as recited in the claims. However, those other references neither disclose nor suggest combining those DNA sequences with a "second heterologous insertion DNA sequence [that] encodes a second gene product that confers resistance to a selection agent involved in the selection of transformants," together in a "DNA construct for homologous recombination," as recited in the pending claims.

For the foregoing reasons Applicants respectfully submit that the pending claims are nonobvious and the rejections for alleged obviousness should be withdrawn.

F. Conclusion

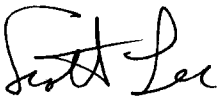
Applicant respectfully submits that claims 71-77 are in condition for allowance. Issuance of a Notice of Allowance is earnestly requested.

If there is any fee due in connection with the filing of this Reply, please charge the fee to our Deposit Account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: May 12, 2009

By: 

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